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Use of transgenic animals in understanding molecular mechanisms of toxicity.

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Understanding molecular mechanisms of chemical toxicity and the potential risks of drugs to man is a pivotal part of the drug development process. With the dramatic increase in the number of new chemical entities arising from high throughput screening, there is an urgent need to develop systems for the rapid evaluation of potential drugs so that those agents which are most likely to be free of adverse effects can be identified at the earliest possible stage in drug development. The complex mechanisms of action of chemical toxins has made it extremely difficult to evaluate the precise toxic mechanism and also the relative role of specific genes in either potentiating or ameliorating the toxic effect. This problem can be addressed by the application of genetic strategies. Such strategies can exploit strain differences in susceptibility to specific toxic agents or, with the rapidly developing technologies, can exploit the use of transgenic animals where specific genes can be manipulated and subsequent effects on chemical toxicity evaluated. Transgenic animals can be exploited in a variety of ways to understand mechanisms of chemical toxicity. For example, a human gene encoding a drug metabolizing enzyme can be directly introduced and the effects on toxic response evaluated. Alternatively, specific genes can be deleted from the mouse genome and the consequences on toxicological response determined. Many toxic chemical agents modulate patterns of gene expression within target cells. This can be used to screen for responses to different types of toxic insult. In such experiments the promotor of a stress-regulated gene can be ligated to a suitable reporter gene, such as lacZ, or green fluorescent protein, and inserted into the genome of an appropriate test species. On administration of a chemical agent, cells which are sensitive to the toxic effects of that chemical will express the reporter, which can then be identified using an appropriate assay system. This latter strategy provides the potential for screening a large number of compounds rapidly for their potential toxic effects and also provides information on tissue and cellular specificity. Experiments using transgenic animals can be complex, and care must be taken to ensure that the results are not affected by background activities within the species being used. For example, the introduction of a specific human cytochrome P450 gene may have no effect on the metabolic disposition of a drug or toxin because of the

background activity within the mouse. As the toxicity of a chemical agent is determined by a wide range of different factors including drug uptake, metabolism, detoxification and repair, differences between man and the species being used could potentially generate a toxic response in the animal model whereas no toxicity may be observed in man. In spite of these confounding factors, the application of transgenic animals to toxicological issues has enormous potential for speeding up the drug discovery process and will undoubtedly become part of this process in the future.

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